Pharmacogenetic Applications and Pharmacogenomic Approaches in Schizophrenia

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Abstract Several genetic factors have been identified that, in combination with clinical and environmental factors, contribute to the variability in response to treatment with antipsychotic drugs. Functional polymorphisms in genes coding for cytochrome-P450 (CYP) enzymes, responsible for the metabolism of over 85 % of drugs, have been associated with the development of drug-induced side-effects, and functional polymorphisms in dopamine and serotonin genes may be associated with adverse reactions and treatment efficacy. Recent estimations have suggested that selecting the drug and clinical dose according to the patient's genetic profile may result in a significant improvement of treatment efficacy (10–15 %) and safety (15–20 %). This information has prompted the development of commercial kits to facilitate the clinical application of pharmacogenetic information. However, prospective studies confirming the

clinical and economical benefits of these tests are required before their widespread implementation in clinical practice.

Keywords Pharmacogenetics · Antipsychotics · CYP · Dopamine · Serotonin · Schizophrenia

Introduction

Schizophrenia, schizoaffective and related disorders are common human disorders, with severe detrimental effects on patients and their caretakers. Treatment of schizophrenia disorders is still far from satisfactory, with up to 30–50 % of patients not responding adequately to pharmacological treatments. Additionally, the antipsychotic drugs used for the treatment of psychotic symptoms induce a number of severe and long-lasting effects. First-generation antipsychotics (FGA, also known as classical or typical antipsychotics), characterised for their strong affinity for dopaminergic receptors, are known to cause extra-pyramidal side-effects (i.e., akathisia and dyskinesias) which may remain after treatment withdrawal. Second-generation or atypical antipsychotics (SGA) have a lower incidence of EPS, but cause other important and severe side-effects (weight gain, diabetes, hypertension, obesity and dyslipidemia amongst others) [1]. Treatment failure and side effects are thought to be caused by a combination of clinical, environmental and genetic factors. Knowledge of these influencing factors may help to improve psychopharmacological treatment and prevent adverse reactions.

Pharmacogenetic studies have proved that antipsychotic treatment variability has an important degree of heritability, although the later has not been quantified through systematic twin studies. Nevertheless, concordance in the response to antipsychotic treatment has been reported in a number of

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twin pairs suggesting a strong genetic contribution [2]. However, it is clear that genetic factors can only partly explain treatment variability, and that clinical and environmental factors have an important contribution to antipsychotic response. Clinical observations such as early treatment response and significant weight gain are linked to good prognosis, whereas early age of onset and presence of extra-pyramidal symptoms predict poor response to antipsychotics [3–5]. Caffeine consumption inhibits the activity of CYP1A2, an enzyme involved in the metabolism of the frequently used antipsychotics olanzapine and clozapine, whereas smoking induces CYP1A2 activity, increasing clearance rates [6]. Co-administration of antipsychotics competing for the same enzyme leads to their inhibition [7], reducing treatment efficacy and increasing side-effects. Other non-genetic factors, including demographic (e.g., gender and ethnic group) and social factors (e.g., family or social support) may also play a role in treatment outcome. Detailed reviews on non-genetic factors influencing antipsychotic response can be found in the literature and are not the scope of this review. These non-genetic factors have complicated the identification of genetic components of treatment variability. Unfortunately, the majority of the pharmacogenetic studies conducted to date had limited clinical and environmental information and their contribution could not be assessed along with the influence of genetic factors. Current strategies include the incorporation of detailed clinical and environmental information in pharmacogenetic studies to elucidate the real influence of genetic variants. Nevertheless, a number of genes containing potentially influential variants have been identified.

Pharmacogenetic (selected candidate genes) and pharmacogenomic (genome-wide investigations) strategies have been used to identify genetic factors related to antipsychotic treatment variability. While most of the findings currently translated into clinical practice have been obtained via pharmacogenetic strategies, pharmacogenomic strategies interrogating the whole genome have revealed novel areas of interest for antipsychotic activity [8]. However, due to the difficulty in collating samples large enough to achieve reliable statistical power, the results of pharmacogenomic studies on antipsychotics need to be confirmed before their implementation in clinical practice and will not be detailed in this review. The following sections will summarise the most significant pharmacogenetic findings and will give an overview of their potential clinical applications.

Pharmacogenetics of Drug Metabolism and Transport

The existence of functional polymorphisms in genes coding for phase I metabolic enzymes has been known since the

1950s, when the effect of one such CYP2D6 polymorphism on debrisoquine metabolism was discovered. Since then a number of functional genetic variants that alter the metabolic activity of enzymes to poor (PM), intermediate (IM) or ultra-rapid (UM) have been described in several enzymes of the hepatic cytochrome P450 (P450). These enzymes are responsible for the metabolism of more than 85 % of xenobiotics, including most psychotropic drugs. Table 1 includes a summary of currently available antipsychotics and their main metabolic pathways. The presence of these functional polymorphisms has been directly related to drug clearance [9], with PM variants associated with higher plasma levels and the UM forms with rapid clearance and lower plasma concentrations of drugs or their metabolites. The work of Kirchheiner and collaborators illustrated the influence of these polymorphisms on antipsychotic dose requirements [10]. The authors showed that individuals who were CYP2D6 or CYP2C19 PMs required significantly lower doses of their substrate antidepressant or antipsychotic drugs than normal extensive metabolizers. In contrast, UM individuals required an increment of up to threefold normal clinical doses to acquire the drug/metabolite plasma levels associated with therapeutic response. Patients treated with antipsychotics with narrow dose ranges are at higher risk of developing movement disorders when carrying copies of PM variants, whereas UM patients are more likely to fail to respond to standard doses of FGA and SGA and may require higher dosages. Interestingly, these polymorphisms display varying frequencies amongst ethnic groups. For example, CYP2D6 individuals are relatively frequent in European Caucasian populations (7–10 %) and relatively infrequent in Asian populations (1–2 %) [11]. Significant geographical variation is also common in other CYP functional polymorphisms and may partially explain the differences in treatment response observed between populations.

Pharmacogenetic studies provide further evidence of the importance of CYP variants on antipsychotic treatment outcome. CYP2D6, CYP1A2 and CYP17A1 functional variants have been related to risk of developing tardive dyskinesia (TD) [12–15] and weight gain [16, 17], although

Table 1 List of main metabolic pathways used to process commonly used antipsychotic drugs

Drug	Type	Metabolic pathway
Aripiprazole	SGA	CYP2D6, CYP3A
Clorpromazine	FGA	CYP2D6, CYP1A2
Haloperidol	FGA	CYP2S6, CYP3A, CYP1A2
Olanzapine	SGA	CYP1A2, CYP2D6
Risperidone	SGA	CYP2D6, CYP3A
Clozapine	SGA	CYP1A2, CYP3A, CYP2D6, CYP2C19

FGA first generation antipsychotic, SGA second generation antipsychotic

findings are not universally replicated [8]. For instance, a study of CYP mutations in a large cohort of patients treated with antipsychotics (the CATIE study) failed to find correlations with clinical outcome [18]. Replication failure is often the result of differences in clinical and environmental characteristics between independent studies [19]. The CATIE study comprised patients treated with a variety of FGA and SGA which may have confounded the analyses. Nevertheless, a recent reanalysis of the study data, stratifying by type of treatment, revealed associations between CYP3A43 polymorphisms and response to olanzapine [20]. Additionally, meta-analyses of CYP findings including positive and negative reports confirm their contribution to adverse reactions [21], although their contribution to treatment efficacy is yet unconfirmed.

Relatively few studies have investigated the contribution of conjugation enzymes (phase II enzymes) on treatment response and no clear association has been reported [8]. However, the number of studies investigating phase II enzymes is relatively modest and further research is required to elucidate their contribution to treatment variability. Finally, antipsychotic drugs display varying degrees of affinity for the P-glycoprotein (PgP, coded by the *ABCB1* gene, [22]), a transmembrane transporter in the blood–brain barrier. Recent studies have shown that *ABCB1* 3435-T allele and *ABCB1* 2667-T/3435-T haplotype carriers were more frequent among subjects without extrapyramidal syndromes [23], suggesting that this transporter protein, involved in brain clearance of antipsychotics, may also contribute to treatment variability.

Pharmacogenetics of Treatment Response

Pharmacogenetic studies on the level of efficacy of antipsychotic treatments have been marred by the difficulty of accurately assessing treatment response and the differing criteria used [8]. Thus, replication failure is common, and contradicting reports are often the norm. Nevertheless, pharmacogenetic studies have confirmed the clinical validity of targeting dopamine and serotonin systems, and shed light on other genes contributing to antipsychotic efficacy.

An average of 60–80 % occupancy of brain dopamine receptors has been linked with therapeutic efficacy, and higher levels of occupancy lead to development of side-effects [24]. All currently available antipsychotics block dopamine receptors to a varying degree. FGA display strong affinity whereas SGA display moderate to high affinity for D2, D3 and D4 receptors. Numerous pharmacogenetic studies confirm the relevance of dopamine receptors for antipsychotic efficacy [2, 8]. Figure 1 summarises the number of published reports associating

Fig. 1 Approximated numbers of published pharmacogenetic studies reporting statistically significant genetic associations with response and adverse reactions

genetic variants (grouped by gene) with level of antipsychotic efficacy. The most significant findings associate a D2 −141-C *Ins/Del* polymorphism with antipsychotic response, with patients carrying the −141-C *Del* variant, associated with lower expression of the receptor protein, presenting poorer response to treatment [25]. Similarly, a D3 Ser9Gly polymorphism has been reported to contribute to treatment variability, with carriers of the high-dopamine affinity Ser9 variant presenting better treatment response [26]. Less consistent findings associate other dopamine variants with treatment efficacy [8].

There is strong evidence supporting the contribution of serotonergic variants to treatment variability. A 5-HT2A promoter region variant, −1438-G, associated with lower expression of the receptor protein [27], and a strongly linked synonymous allele, 102-C, are increased in patients not responding to the SGA clozapine, risperidone and olanzapine [8, 28]. Similarly, a 5-HT2A 452Tyr variant, with reduced ability to activate phospholipases C and D [29], is reportedly more frequent in non-responding patients. Polymorphic variants in 5-HT1A, 5-HT2C, 5-HT3A and 5-HT6 also contribute to drug efficacy [30–37], reinforcing the relevance of the serotonergic system in antipsychotic activity.

Minor contribution of genetic variants in other targeted neurotransmitter systems has been reported, including reports of association between polymorphisms in glutamatergic (GRM3) [38] and histaminic (H2, H3) [31, 39] receptor genes. This evidence suggests that these systems play a minor role in the mechanism of action of currently available antipsychotics. Nevertheless, this does not invalidate the potential therapeutic validity of these and other neurotransmitter systems, which may be the target of

novel drugs. Finally, a number of polymorphisms in genes related to the aetiology of the disease (ZNF804, DTNBP1, NRG1) [40–43], metabolism of neurotransmitters (BDNF, COMT) [44–46], cellular development, signalling, transport and other functions (AKAP13, CACNA1, GRIA1, GRIA2, GRIA4, GHRL, NRXN1) [43, 47–51] have also been reported in association with response. However, these findings have yet to be confirmed in independent studies.

It is important to note that none of the associations described in this section have been widely replicated. Phenotype variability and environmental influences are confounding factors that interfere with the identification of genetic associations both related to drug metabolism and drug response and induce false negative and false positive results. An alternative reason behind replication failure of response findings is the use of indirect markers. Many of the response-associated polymorphisms do not have a significant functional effect, and may act as indirect indicators of causal polymorphisms to which they are linked. The linkage status may vary in different populations and thus the magnitude and/or the direction of the associations may change. Additionally, the genetic effects observed are moderate to low (odds ratios generally below 2), inferior to the values observed in the associations with functional metabolic polymorphisms. Treatment response is a complex phenotype that may be determined, in addition to environmental factors, by several contributing genes from drug targets and interacting proteins, in contrast with drug metabolism which is mainly determined by enzymatic activity. Therefore it is not surprising that the associations are not as clear, which diminishes their clinical value and applicability. Nevertheless, these findings provide important information on the therapeutic value of currently-available drug targets and may help in the design of improved novel antipsychotics.

Pharmacogenetics of Antipsychotic-Induced Side-Effects

FGA and SGA produce important and long-lasting side-effects with negative effects both in terms of prognosis and treatment compliance. Adverse reaction phenotypes are relatively easy to determine, which facilitates the identification of related genetic factors.

Weight gain and other effects contributing to metabolic syndrome (obesity, diabetes, hypertension, and cardiovascular events) are considered the most important antipsychotic-induced side-effects, and are observed in up to 57 % patients treated with SGA, and 17 % treated with FGA. Serotonin regulates feeding behaviour and alterations in serotonin transmission have been suggested to contribute to antipsychotic-induced weight gain. Several studies associating

polymorphisms in serotonin receptors with weight gain support this hypothesis. The most significant finding associates a 5-HT_{2C} gene polymorphism, –759-T/C, with weight-gain and BMI, although the direction of the association varies in different studies [17, 52, 53]. A meta-analysis confirmed the protective effects of the –759-T allele against weight gain in Caucasian patients [54]. Several reports implicate genes involved in energy intake and expenditure, namely leptin (LEP) [55–58] and melanocortin receptor 4 (MC4R) [59, 60], in antipsychotic induced weight gain, thus suggesting a multigenic cause of this effect. Other energy regulatory genes, including INSIG2 and GHRL have also been associated with weight gain in unconfirmed reports [49, 61].

TD is a severe and long-lasting side-effect associated mainly with the use of FGA, and to a minor extent with some SGA (i.e., risperidone). Patients presenting *CYP2D6* PM alleles and D2 variants associated with lower receptor expression, resulting in higher receptor occupancy, are at higher risk of developing TD [25, 62, 63]. 5-HT_{2C} and 5-HT_{2A} low expression variants have also been associated with TD development, especially when considering the age of the patient, probably reflecting an indirect influence on dopamine regulation [64–66].

The genetic effects observed in these studies are moderate to high, suggesting a potential clinical applicability. However, confirmation of the direction and predictive value of the findings in different population groups is required before the clinical application of this information. Interestingly, the number of genes associated with the development of side-effects surpasses the number of genes associated with treatment efficacy (see Fig. 1), reinforcing the need for novel drugs directed to targets of proven clinical value.

Pharmacogenetic Applications

The ultimate goal of pharmacogenetic research is the use of genetic information for the personalisation of treatment. However, few of the reported findings have been translated into clinical applications in spite of their potential benefits.

The implications of CYP findings for antipsychotic treatment are clear. Characterising the genetically-determined CYP status of the patients before the start of the treatment may provide useful and beneficial information. Estimations of the clinical and economical benefits of CYP genetic testing support their implementation in clinical practice. It has been suggested that the adjustment of clinical doses according to the individuals' genetic profile may result in a 10–15 % improvement in the level of efficacy and in 15–20 % reductions in side-effects. Unfortunately, this information is not yet widely used in clinical practice. The clinical value of genetic information on drug targets is not yet clearly established. Most of the reported associations with

drug target variants have a limited predictive value and cannot be used as single-markers of response or side-effects. Although attempts have been made at combining information in several genes to improve prediction values, further research on their clinical validity is required.

Several tests for the genetic determination of the metabolic status of patients, prediction of the level of efficacy, and risk of developing side-effects are already available in commercial and clinical laboratories (see Table 2 for summary list). CYP functional polymorphisms aside, most of these tests are of limited predictive value, never reaching 100 % certainty (and far from it). This is not surprising given that the majority of the tests do not consider the clinical and environmental factors that play a role in treatment variability, and include unconfirmed genetic findings. Nevertheless, the information contained in these tests has the potential to improve treatment response by helping to select the most beneficial treatment at the right dose for patients according to their genetic predisposition. In spite of this, the use of genetic tests to assist drug selection in psychiatry is minimal. Lack of information and limited access to clinical or reference laboratories with capabilities for pharmacogenetic testing are partly to blame. However, the main reason that may hinder the use of pharmacogenetic tests is the lack of supporting research assessing the benefits. To date, no study has investigated if the adjustment of clinical doses according to

the patient's CYP genetic variants results in a reduction of the incidence of side-effects, and in an improvement of response. Similarly, no prospective study has proved that the use of pharmacogenetic prediction tests for the selection of drug type positively influences the level of efficacy that is reflected in a reduction of hospitalization time, improvement of social functioning, etc. Thus, there is little supporting evidence encouraging the use of pharmacogenetic information in clinical settings. Without a prospective trial to prove the clinical and economical benefits of using genetic information to aid drug and dose selection, clinicians are right to doubt the benefits of a pharmacogenetic approach. The affluence of commercial tests offering a variety of genetic information, sometimes poorly translated into clinically useful information, reinforces the need for prospective validating studies.

Conclusion

Pharmacogenetic and Pharmacogenomic studies have identified several genetic factors that, in combination with clinical and environmental events, contribute to the variability in response to treatment with antipsychotic drugs. Functional genetic variants in CYP metabolising enzymes are the most promising findings, with the potential to improve drug safety and efficacy. Findings in drug targets require further research, but may be valuable for the risk evaluation of side-effects. Findings relating genetic variants with treatment response have a limited predictive and clinical value, especially in absence of environmental and clinical information. In spite of the supporting evidence, pharmacogenetic testing is not widely used in psychiatric practice. Prospective studies evaluating the clinical and economical benefits may convince the clinicians of the value of pharmacogenetic information for the improvement of antipsychotic efficacy and safety.

Future research in the field will investigate the influence of clinical and environmental factors, along with genetic factors, to better determine their contribution to antipsychotic efficacy. Genomic and epigenetic studies may also reveal novel genetic areas of interest for antipsychotic activity.

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Table 2 List of available pharmacogenetic tests for selected antipsychotic drugs

Test	Information provided	Manufactured
Amplichip	CYP2D6 and CYP2C19 polymorphisms	Roche
Tm Tag-it Mutation detection kit	CYP2D6 and CYP2C19 most common polymorphisms	TMBIOSCIENCES-Luminex
Vercode ADME core panel	CYP450 enzymes and polymorphisms in other metabolic enzymes	Illumina
DMET Plus premier pack	1,936 markers in metabolizing genes	Affymetrix
Genecept assay	Polymorphisms CYP2D6, CYP2C19, SLC6A4, DRD2, AnkirynG, COMT and MTHFR genes	Genomind
GeneSightRx	Polymorphisms in CYP2D6, CYP2C19, CYP2C9, CYP1A2, SLC6A4 and HTR2A genes	AssureRx
BrainChip	Polymorphisms in CYP enzymes and drug target genes	Brainco
Neurofarmagen	Polymorphisms in CYP enzymes and drug target genes	AB Biotics

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